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EXAMINER	
FORMAN, BETTY J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/297,668	Applicant(s) GERSHONI ET AL.
	Examiner BJ Forman	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *144-182* is/are pending in the application.

4a) Of the above claim(s) *157-158 171-176 178 180-182* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *144-156,159-170,177 and 179* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This action is in response to papers filed 22 July 2002 in Paper No. 17 in which claim 159 was amended and new claims 177-182 were added. All of the amendments have been thoroughly reviewed and entered. New Claims 178 and 180-182 depend from a non-elected inventions and therefore are not drawn to elected inventions. Claims 178 and 180-182 are withdrawn from consideration as being drawn to non-elected inventions. The previous rejections in the Office Action of Paper No. 16 dated 21 February 2002 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) are maintained. All of the arguments have been thoroughly reviewed and are discussed below. New grounds for rejection necessitated by amendment are discussed.

Applicant Affirmation of the election with traverse is acknowledged. The traversal is on the grounds that the special technical feature of the present invention is not disclosed by Marks because the biological unit of Marks is a single antibody which contains a heavy chain fragment and a light chain fragment. Applicant argues that the two fragments of a single antibody cannot be randomly ligated as instantly claimed.

The argument has been considered but is not found persuasive because Marks specifically teaches randomly ligating at least two DNA fragments (Fig. 1, line 11-end). The claims are drawn to a method of identifying and producing a peptide, the method comprising: providing a plurality of DNA fragments which appear in a DNA sequence which encode a single biological unit and creating a library of oligonucleotides each comprising at least two of said fragments being randomly ligated. Marks discloses the claimed method wherein the biological unit is an antibody wherein antibody fragments are randomly ligated, inserted into an expression system, expressed as peptides, screened, identified and producing identified peptides (page 16008). Therefore, Marks discloses the technical feature which link Groups I-

V. Hence, the groups are not so linked as to form a single general inventive concept as defined by PCT Rule 13.1.

The restriction is still deemed proper and therefore made FINAL.

Claims 144-156, 159-170, 177 and 179 are under prosecution.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 144-146, 149-151, 155, 156, 159-161, 163-165, 169 and 170 are rejected under 35 U.S.C. 102(b) as being anticipated by Huse et al (Science, 1989, 246: 1275-1281).

Regarding Claim 144, Huse et al disclose a method of identifying and producing a peptide which interacts with a ligand which interacts with a discontinuous epitope of a single biological unit comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph). The courts have stated that claims must be given their broadest

reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). The claims are given the broadest reasonable interpretation consistent with the claim language and specification wherein "a single biological unit" is not clearly defined. Given the broadest reasonable interpretation of the claim, the claimed single biological unit encompasses the antibody of Huse et al. Therefore, Huse et al disclose the method as claimed.

Regarding Claim 145, Huse et al disclose the method wherein step (a) comprises cutting said DNA sequence to form said plurality of DNA fragments (page 1278, left column, first full paragraph).

Regarding Claim 146, Huse et al disclose the method wherein said cutting is accomplished enzymatically i.e. restriction digestion (page 1278, left column, first full paragraph).

Regarding Claim 149, Huse et al disclose the method wherein step (b) comprises randomly ligating said plurality of DNA fragments to form at least one ligated fragment and at least partially digesting the ligated fragment to form said library i.e. the light chain fragments and heavy chain fragments are each randomly ligated into vectors and then digested (page 1277, right column, last three lines-page 1278, first three lines).

Regarding Claim 150, Huse et al disclose the method wherein said expression system comprises a plurality of bacteria and step (c) comprises inserting one of said library into each of said plurality of bacteria (page 1278, left column, first full paragraph).

Regarding Claim 151, Huse et al disclose the method wherein said expression system comprises a plurality of phage and step (c) comprises inserting one of said library into each of said plurality of phage (page 1278, left column, first full paragraph).

Regarding Claim 155, Huse et al disclose the method wherein the single biological unit is a protein i.e. the single biological unit is an antibody and the fragments provided in (a) are fragments of the antibody (Abstract). The claims are given the broadest reasonable interpretation consistent with the claim language and specification wherein "a single biological unit" is not clearly defined. Given the broadest reasonable interpretation of the claim, the claimed single biological unit encompasses the antibody of Huse et al. Therefore, Huse et al disclose the method as claimed.

Regarding Claim 156, Huse et al disclose the method wherein the single biological unit is two or more proteins which interact to form a complex i.e. the single biological unit is a light chain and a heavy chain and the light and heavy chain interact to form an antibody complex (Abstract). The claims are given the broadest reasonable interpretation consistent with the claim language and specification wherein "a single biological unit" is not clearly defined. Given the broadest reasonable interpretation of the claim, the claimed single biological unit comprising two or more proteins encompasses the light chain and heavy chain of Huse et al. Therefore, Huse et al disclose the method as claimed.

Regarding Claim 159, Huse et al disclose a method of preparing a library of peptides comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph). The claims are given the broadest reasonable interpretation consistent with the claim language and specification wherein "a single biological unit" is not clearly defined. Given

the broadest reasonable interpretation of the claim, a single biological unit encompasses the antibody of Huse et al. Therefore, Huse et al disclose the method as claimed.

Regarding Claim 160, Huse et al disclose the method wherein step (a) comprises cutting said DNA sequence to form said plurality of DNA fragments (page 1278, left column, first full paragraph).

Regarding Claim 161, Huse et al disclose the method wherein said cutting is accomplished enzymatically i.e. restriction digestion (page 1278, left column, first full paragraph).

Regarding Claim 163, Huse et al disclose the method wherein step (b) comprises randomly ligating said plurality of DNA fragments to form at least one ligated fragment and at least partially digesting the ligated fragment to form said library i.e. the light chain fragments and heavy chain fragments were each randomly ligated into vectors and then digested (page 1277, right column, last three lines-page 1278, first three lines).

Regarding Claim 164, Huse et al disclose the method wherein said expression system comprises a plurality of bacteria and step (c) comprises inserting one of said library into each of said plurality of bacteria (page 1278, left column, first full paragraph).

Regarding Claim 165, Huse et al disclose the method wherein said expression system comprises a plurality of phage and step (c) comprises inserting one of said library into each of said plurality of phage (page 1278, left column, first full paragraph).

Regarding Claim 169, Huse et al disclose the method wherein the single biological unit is a protein i.e. the single biological unit is an antibody and the fragments provide in (a) are fragments of the antibody (Abstract). The claims are given the broadest reasonable interpretation consistent with the claim language and specification wherein "a single biological unit" is not clearly defined. Given the broadest reasonable interpretation, the claimed single biological unit encompasses the antibody of Huse et al. Therefore, Huse et al disclose the method as claimed.

Regarding Claim 170, Huse et al disclose the method wherein the single biological unit is two or more proteins which interact to form a complex i.e. the single biological unit is f a light chain and a heavy chain which interact to from an antibody complex (Abstract). The claims are given the broadest reasonable interpretation consistent with the claim language and specification wherein "a single biological unit" is not clearly defined. Given the broadest reasonable interpretation, the claimed single biological unit encompasses the light chain and heavy chain proteins of Huse et al. Therefore, Huse et al disclose the method as claimed.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 147, 148, 154, 162 and 168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huse et al (Science, 1989, 246: 1275-1281) in view of Stemmer et al (U.S. Patent No. 5,811,238, filed 30 November 1995).

Regarding Claim 147, Huse et al teach a method of identifying and producing a peptide which interacts with a ligand which interacts with a discontinuous epitope of a single biological unit comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the

identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph) wherein said cutting is accomplished enzymatically i.e. restriction digestion (page 1278, left column, first full paragraph) but they do note teach the cutting is accomplished by mechanically cutting. However, mechanical cutting of DNA was well know in the art at the time the claimed invention was made as taught by Stemmer et al. who teach a similar method of identifying and producing a peptide. Specifically, Stemmer et al teach the similar method comprising providing a plurality of DNA fragments which appear in a DNA sequence encoding a single biological unit (i.e. antibody); creating a library of oligonucleotides by randomly rearranging said fragments (i.e. shuffling); inserting the oligonucleotides into an expression system; expressing and screening the expressed peptide (Column 5, lines 23-50) wherein the fragments are provided by mechanically cutting (Column 17, lines 30-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the enzyme digestion of Huse et al with the mechanical shearing as taught by Stemmer et al to thereby eliminate the time and labor involved with DNA digestion and DNA purification following digestion for the obvious benefit of economy of time and labor.

Regarding Claim 148, Huse et al teach the method wherein said fragments are provide by cutting i.e. restriction digestion (page 1278, left column, first full paragraph) but they do not teach the fragments are provided by synthesis. However, synthesis of DNA fragments was well know in the art at the time the claimed invention was made as taught by Stemmer et al. who teach a similar method of identifying and producing a peptide. Specifically, Stemmer et al teach a similar method comprising providing a plurality of DNA fragments which appear in a DNA sequence encoding a single biological unit (i.e. antibody); creating a library of oligonucleotides by randomly rearranging said fragments (i.e. shuffling); inserting the oligonucleotides into an expression system; expressing and screening the expressed peptide (Column 5, lines 23-50) wherein the fragments are synthesized (Column 17, lines 48-52). It would have been obvious to one of ordinary skill in the art at the time the claimed invention

was made to modify the enzyme digestion of Huse et al with the synthesis as taught by Stemmer et al to thereby provide fragments of known sequence and for the obvious benefit of screening known fragments for binding activity. For example, a protein having a known sequence interacts with a ligand, but the fragment of protein which interacts with the ligand is unknown. The skilled artisan would have been motivated to analyze the encoding sequence to identify fragments encoding potential binding activity and to synthesize only those specific fragments and to randomly ligate the fragments to thereby identify and produce discontinuous peptides with bind to the ligand of interest.

Regarding Claim 154, Huse et al teach the method wherein said expression system comprises a plurality of bacteria and step (c) of inserting comprises inserting one of said library into each of said plurality of bacteria (page 1278, left column, first full paragraph) but they do not teach the expression system is eukaryotic. However, eukaryotic expression systems were well known in the art at the time the claimed invention was made as taught by Stemmer et al who teach the similar method wherein the expression system is eukaryotic (Column 38, lines 1-42). Additionally, they teach that eukaryotic systems are preferred because the peptide produced in secreted as an intact product (Column 38, lines 5-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the phage expression system of Huse et al with the eukaryotic expression system as taught by Stemmer et al and to insert the library of oligonucleotides into eukaryotic vectors for expression in a eukaryotic cell to thereby express and secret intact peptides as preferred by Stemmer et al for the obvious benefit of obtaining an intact peptide which is secreted and therefore easily purified as taught by Stemmer et al (Column 38, lines 5-10).

Regarding Claim 162, Huse et al teach a method preparing a peptide library comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression

system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph) wherein said cutting is accomplished enzymatically i.e. restriction digestion (page 1278, left column, first full paragraph) but they do note teach the cutting is accomplished by mechanically cutting. However, mechanical cutting of DNA was well know in the art at the time the claimed invention was made as taught by Stemmer et al. who teach a similar method of identifying and producing a peptide. Specifically, Stemmer et al teach the similar method comprising providing a plurality of DNA fragments which appear in a DNA sequence encoding a single biological unit (i.e. antibody); creating a library of oligonucleotides by randomly rearranging said fragments (i.e. shuffling); inserting the oligonucleotides into an expression system; expressing and screening the expressed peptide (Column 5, lines 23-50) wherein the fragments are provided by mechanically cutting (Column 17, lines 30-35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the enzyme digestion of Huse et al with the mechanical shearing as taught by Stemmer et al to thereby eliminate the time and labor involved with DNA digestion and DNA purification following digestion for the obvious benefit of economy of time and labor.

Regarding Claim 168, Huse et al teach the method wherein said expression system comprises a plurality of bacteria and step (c) of inserting comprises inserting one of said library into each of said plurality of bacteria (page 1278, left column, first full paragraph) but they do not teach the expression system is eukaryotic. However, eukaryotic expression systems were well known in the art at the time the claimed invention was made as taught by Stemmer et al who teach the similar method wherein the expression system is eukaryotic (Column 38, lines 1-42). Additionally, they teach that eukaryotic systems are preferred because the peptide produced in secreted as an intact product (Column 38, lines 5-10). It would have been obvious

to one of ordinary skill in the art at the time the claimed invention was made to modify the phage expression system of Huse et al with the eukaryotic expression system as taught by Stemmer et al and to insert the library of oligonucleotides into eukaryotic vectors for expression in a eukaryotic cell to thereby express and secret intact peptides as preferred by Stemmer et al for the obvious benefit of obtaining an intact peptide which is secreted and therefore easily purified, as taught by Stemmer et al (Column 38, lines 5-10).

6. Claims 152, 153, 166 and 167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huse et al (Science, 1989, 246: 1275-1281) in view of Marks et al (The Journal of Biological Chemistry, 1992, 267(23): 16007-16010).

Regarding Claims 152 and 153, Huse et al teach a method of identifying and producing a peptide which interacts with a ligand which interacts with a discontinuous epitope of a single biological unit comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide wherein the oligonucleotides are inserted into said phage by cloning (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph) but they do note teach the oligonucleotides are cloned into phage genes coding for a coat protein. Marks et al teach a similar method comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. antibody);

creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide wherein the oligonucleotides are inserted into said phage by cloning (page 16008, Fig 1 and 2) wherein the said oligonucleotides are inserted into phage genes coding for a coat protein and wherein said coat protein is pIII or pVIII (page 16008, Fig. 2). Additionally, Marks et al teach that by inserting the oligonucleotide in to the coat proteins (e.g. pIII or pVIII) multiple antibodies are displayed on each phage providing higher binding avidity thereby maintaining antibody-antigen binding during washing even for the lower-affinity binding reactions (page 16009, left column, first paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the phage in the method of Huse et al by inserting the oligonucleotide in to either the pIII or pVIII coat protein of filamentous phage as taught by Marks et al to thereby express multiple antibodies on each phage and increase binding avidity thereby maintaining antibody-antigen binding during washing and selection steps for the expected benefit of obtaining even lower-affinity binding reactions as taught by Marks et al (page 16009, left column, first paragraph).

Regarding Claims 166 and 167, Huse et al teach a method preparing a peptide library comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide wherein the oligonucleotides are inserted into said phage by cloning (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph) but they do not

teach the oligonucleotides are cloned into phage genes coding for a coat protein. Marks et al teach a similar method comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide wherein the oligonucleotides are inserted into said phage by cloning (page 16008, Fig 1 and 2) wherein the said oligonucleotides are inserted into phage genes coding for a coat protein and wherein said coat protein is pIII or pVIII (page 16008, Fig. 2). Additionally, Marks et al teach that by inserting the oligonucleotide in to the coat proteins (e.g. pIII or pVIII) multiple antibodies are displayed on each phage providing higher binding avidity thereby maintaining antibody-antigen binding during washing even for the lower-affinity binding reactions (page 16009, left column, first paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the phage in the method of Huse et al by inserting the oligonucleotide in to either the pIII or pVIII coat protein of filamentous phage as taught by Marks et al to thereby express multiple antibodies on each phage and increase binding avidity thereby maintaining antibody-antigen binding during washing and selection steps for the expected benefit of obtaining even low-affinity binding reactions as taught by Marks et al (page 16009, left column, first paragraph) and thereby produce a more complete library as desired.

NEW CLAIMS

7. Claims 177 and 179 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huse et al (Science, 1989, 246: 1275-1281) in view of Stemmer et al (U.S. Patent No. 5,811,238, filed 30 November 1995).

Regarding Claim 177, Huse et al teach the method of Claims 144 comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph) but they do not teach the DNA fragments have a size of about 50 to about 150 base pairs. However, random ligation of DNA fragments having a size of about 50 to about 150 base pairs was well known in the art at the time the claimed invention was made as taught by Stemmer et al (Column 5, lines 21-50) who specifically teach that the preferred fragment length is <u>about</u> 50 to 150 base pairs (Column 17, lines 21-23). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the fragments of Huse et al using routine experimentation and to derive fragments (e.g. of about 50 to about 150) for the obvious benefits of optimizing fragment length to thereby maximize identification and production of desired peptides. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 179, Huse et al teach the method of Claim 159 comprising: providing a plurality of DNA fragments which appear in a DNA sequence encoding said single biological unit (i.e. Fab antibody); creating a library of oligonucleotides comprising at least two randomly

ligated DNA fragments; inserting each of said oligonucleotides in to an expression system (i.e. phage); expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope (i.e. antigen); identifying the peptide and producing the identified peptide (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph) but they do not teach the DNA fragments have a size of about 50 to about 150 base pairs. However, random ligation of DNA fragments having a size of about 50 to about 150 base pairs was well known in the art at the time the claimed invention was made as taught by Stemmer et al (Column 5, lines 21-50) who specifically teach that the preferred fragment length is <u>about</u> 50 to 150 base pairs (Column 17, lines 21-23). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the fragments of Huse et al using routine experimentation and to derive fragments (e.g. of about 50 to about 150) for the obvious benefits of optimizing fragment length to thereby maximize library preparation. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Response to Arguments

8. Applicant argues that Huse does not create combinations to generate novel structures derived from a single polypeptide and thus does not deal with any tertiary structures. Applicant further argues that the methodology of Huse maintains the integrity of each polypeptide component and ensures the natural position of their fragments as found in nature. In contrast, Applicant states, the instant invention is based on generating novel primary structures to simulate functional tertiary surfaces.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., generating

"novel structures derived from a single polypeptide" and generation of "novel primary structures to simulate functional tertiary surfaces") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims are drawn to method of identifying and producing a peptide and method of preparing a library of peptides, the methods comprising the steps of providing a plurality of DNA fragments which encode a single biological unit, creating a library of oligonucleotides each comprising at least two fragments being randomly ligated, inserting the oligonucleotides in to an expression system, expressing the oligonucleotides to provide peptides, screening the peptides, identifying and producing the peptides. Huse et al (as detailed above) disclose the method as claimed (page 1277, right column, first full paragraph and Fig. 1; and page 1278, left column, first full paragraph).

Applicant argues that step (b) of their method requires that the at least two DNA fragments of step (a) be randomly ligated and because Huse only produces two fragments (which Applicant asserts cannot be randomly ligated), they cannot meet the limitations of step (b). The argument has been considered but is not found persuasive because Huse specifically teach random combination of fragments thereby producing a library (page 1277, right column, first full paragraph and page 1278, left column, first full paragraph).

Applicant argues that the library of Huse contains a lot more than ligated fragments from a single biological unit because it contains ligated fragments from an entire library of biological units. The argument has been considered but is not found persuasive because the open claim language "comprising" encompasses additional biological units. Additionally, step (a) recites "providing a plurality of DNA fragments, which fragments appear in a DNA sequence which encodes a single biological unit". This recitation defines a plurality of DNA fragments but does not limit presence of other DNA fragments which encode other biological units.

Applicant argues that the oligonucleotides of Huse contain two fragments from a single biological unit i.e. a light chain and a heavy chain and Huse does not contemplate putting the fragments in a different order. Therefore, Applicant argues the fragments of Huse cannot be randomly ligated. The argument has been considered but is not found persuasive because Huse specifically teach random combination of fragments thereby producing a library (page 1277, right column, first full paragraph and page 1278, left column, first full paragraph). Additionally, the argument is not considered persuasive because the claims recite "randomly ligated" which does not limit the order or arrangement of the ligated fragments.

Applicant argues that Stemmer does not supply the deficiencies of Huse and therefore the combination of Stemmer and Huse does not make the instant invention obvious. The argument has been considered but is not found persuasive for the reasons state above i.e. Huse discloses the methods as claimed in Claims 144 and 159.

Applicant argues that Marks does not supply the deficiencies of Huse and therefore the combination of Marks and Huse does not make the instant invention obvious. The argument has been considered but is not found persuasive for the reasons state above i.e. Huse discloses the methods as claimed in Claims 144 and 159.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
October 10, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600